Psychotropic drugs and homicide: a prospective cohort study from Finland

After a high-profile homicide case, there is often discussion in the media on whether or not the killing was caused or facilitated by a psychotropic medication. Antidepressants have especially been blamed by non-scientific organizations for a large number of senseless acts of violence, e.g., 13 school shootings in the last decade in the U.S. and Finland (1). In September 2014, there were more than 139,000 hits from Google for the search terms "antidepressant, homicide", and more than 1,050,000 hits for the terms "antidepressant, violence". It is likely that such massive publicity in the lay media has already led a number of patients and physicians to abstain from antidepressant treatment, due to the perceived fear of pharmacologically induced violence.

What is the scientific evidence for an association between psychotropic drugs and homicidal behavior? Most of the available studies are case reports that only suggest a coincidental link between violence or homicide and antidepressants (2,3) or benzodiazepines (4), while very little is known about the association between antipsychotics and homicide. Two recent ecological studies found no support for a significant role of antidepressant use in lethal violence in the Netherlands or the U.S., although data on individual offenders were not available (5,6). Quantitative data from the U.S. Food and Drug Administration (FDA) adverse event reporting system (7) imply that some antidepressants may be associated with a disproportionately high number of violent events (8). On the contrary, two small studies on antidepressant use among a special subgroup of homicide-suicide offenders found no evidence to support a causal link between antidepressants and homicidal behavior (9,10).

There are three crucial conditions that must be fulfilled to properly study the putative association between exposure (i.e., use of a psychotropic drug) and outcome (homicide): a) the sample must be unselected, to be representative of the total offender population; b) the reason for prescribing the medication must be considered and controlled, and c) the effect of other concomitant medication(s) must be adjusted. No such studies have been done thus far on the association between the risk of committing homicide and the use of psychotropic drugs.

We carried out a prospective cohort study with an embedded case-control design in order to test the hypothesis that current antidepressant treatment is associated with an increased risk of committing a homicide. We prospectively collected a database that included all homicides reported to, and investigated by, the police in Finland in the period 2003-2011 (11). From the 1091 homicides known to police, after exclusion of 12 cases not solved, 7 offenders coming from abroad, 24 offenders whose data were blocked due to security reasons, and 10 offenders excluded due to incomplete data on previous incarceration, we were left with 959 offenders, who were included in our analysis. For each offender, 10 population controls where picked from the Population Information System by matching individuals by gender, age (year of birth), and home municipality at the time of each homicide.

Information on medication use from January 1995 to December 2011 was obtained for all cases and their controls through record linkage to the nationwide Finnish Prescription Register. The database contains the date of prescription purchase, the Anatomic Therapeutic Chemical (ATC) code, and the purchased quantity, stated as the number of defined daily doses (DDDs), which are defined by the World Health Organization (12). This procedure has been described in more detail in our previous cohort studies (13-16).

We identified a subject as a "current user" if (s)he was using a given drug at the time of the homicide/matching, according to the amount of medication purchased in DDDs. Drug exposure was assumed to start at the date of purchase, and drug exposure duration was determined by the amount of DDDs. Previous use (Yes/No) was also based on the date of purchase and amount in DDDs. A subject had previous use if (s)he made a prescription purchase during the previous 7-year period, before the time of homicide/matching, but the drug exposure ended before the date of homicide. Among those offenders who had been in prison during the 7-year period prior to homicide, the time during their prison sentence (prior to their release) was censored, and also among their matched control subjects. Subjects aged 25 years or younger were further investigated in a separate analysis.

The primary outcome measure was the risk of offending during current use vs. no current use for three major categories of psychotropic medications: antidepressants, benzodiazepines, and antipsychotics. Within the offender cohort, each individual served as his/her own control. In this analysis, individuals without any medication exposure were omitted. A Poisson regression model was used to estimate the relative risk (RR) of homicide during current use versus no-use of each study medication among the offenders.

The follow-up time on medication was based on DDDs, and truncated to each person's total follow-up time. The RR was calculated for both the adjusted and unadjusted models, according to age, gender, current use of illegal drugs, current use of alcohol, and both current (i.e., at the time of the homicide) and previous use of other study

medications. When comparing offenders and matched controls, the odds ratio (OR) was used as a measure for the risk, and it was estimated using the conditional logistic regression model that takes into account the matching sets (which individuals served as controls for each offender).

For primary outcome measures, the level of statistical significance was set to $p<0.016$ to account for multiple testing (Bonferroni correction). The secondary analysis compared the current vs. no current use of seven other medication categories (opioid analgesics, other analgesics, antiepileptics, lithium, stimulants, medicines used in addictive disorders, other anxiolytics), which were used as covariates in the primary analysis. The level of significance in the secondary analysis was set to $p<0.005$.

The median age of offenders and controls was 36.3 years (range 13.3-88.0 years). A total of 849 (88.5%) offenders were males, and 42 (4.4%) had more than one victim, 761 (79.4%) were intoxicated by alcohol and 51 (5.3%) by illicit drugs during the offence (as confirmed by the police).

The analysis within the offender population revealed that the adjusted RR was 1.31 (95% CI: 1.04-1.65; $p=0.022$) for current use vs. no current use of antidepressants, 1.45 (95% CI: 1.17-1.81; $p=0.001$) for current use vs. no current use of benzodiazepines, and 1.10 (95% CI: 0.82-1.47; $p=0.54$) for current use vs. no current use of antipsychotics. The current use of both opioid (1.92; 95% CI: 1.36-2.72, $p<0.001$) and non-opioid (3.06; 95% CI: 1.78-5.24, $p<0.001$) analgesics was associated with significantly increased risk of offending. Among subjects aged 25 or younger, the only findings approaching statistical significance were observed for current use of opioid analgesics (adjusted RR 3.23; 95% CI: 1.05-9.94; $p=0.04$) and benzodiazepines (adjusted RR 1.95, 95% CI: 0.95-4.00, $p=0.07$). No significant interactions were observed between current use of psychotropic medications vs. intoxication by alcohol or illicit drugs.

The analysis based on case-control design showed an adjusted OR of 1.30 (95% CI: 0.97-1.75) as the risk of homicide for the current use of an antidepressant, 2.52 (95% CI: 1.90-3.35) for benzodiazepines, 0.62 (95% CI: 0.41-0.93) for antipsychotics, and 2.16 (95% CI: 1.41-3.30) for opioid analgesics.

The results of this prospective study show that antidepressant use *per se* was associated with an only modestly increased risk of committing a homicide, with borderline statistical significance. Benzodiazepine and analgesic use was linked with a higher risk of homicidal offending, and the findings remained highly significant even after correction for multiple comparisons.

These results – which may probably be generalized to other developed and stable societies that have a low to medium homicide rate, although not necessarily to countries with higher rates of organized and premeditated crime – imply that the use of antidepressants should not be denied to either adults or adolescents due to a presumed risk of homicidal behavior. The surprisingly high risk associated with opioid and non-opioid analgesics deserves further attention in the treatment of pain among individuals with criminal history.

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